CLAIMS

1. A method of inhibiting secretion from a non-neuronal cell comprising administering an agent comprising at least first and second domains, wherein the first domain cleaves one or more proteins essential to exocytosis and the second domain translocates the first domain into the cell.

2. A method according to Claim 1, for treatment of disease caused, exacerbated or maintained by secretion from a non-neuronal cell or non-neuronal cells.

3. A method according to Claim 1 or 2, wherein the agent further comprises a third domain for targeting the agent to a non-neuronal cell.

4. A method according to Claim 3 wherein the third domain targets the agent to an endocrine cell.

5. A method according to Claim 4 wherein the third domain comprises or consists of a ligand selected from iodine; thyroid stimulating hormone (TSH); TSH receptor antibodies; antibodies to the islet-specific monosialo-ganglioside GM2-1; insulin, insulin-like growth factor and antibodies to the receptors of both; TSH releasing hormone (protirelin) and antibodies to its receptor; FSH/LH releasing hormone (gonadorelin) and antibodies to its receptor; corticotrophin releasing hormone (CRH) and antibodies to its receptor; and ACTH and antibodies to its receptor.

6. A method according to Claim 4 or 5 for the treatment of a disease caused, exacerbated, or maintained by secretion from an endocrine cell, preferably for treatment of a disease selected from endocrine neoplasia including MEN; thyrotoxicosis and other diseases dependent on

hypersecretions from the thyroid; acromegaly, hyperprolactinaemia, Cushings disease and other diseases dependent on anterior pituitary hypersecretion; hyperandrogenism, chronic anovulation and other diseases associated with polycystic ovarian syndrome.

7. A method according to Claim 3 wherein the third domain targets the agent to inflammatory cells

8. A method according to Claim 7 wherein the third domain comprises or consists of a ligand selected from (i) for mast cells, complement receptors in general, including C4 domain of the Fc IgE, and antibodies/ligands to the C3a/C4a-R complement receptor; (ii) for eosinophils, antibodies/ligands to the C3a/C4a-R complement receptor, anti VLA-4 monoclonal antibody, anti-IL5 receptor, antigens or antibodies reactive toward CR4 complement receptor; (iii) for macrophages and monocytes, macrophage stimulating factor, (iv) for macrophages, monocytes and neutrophils, bacterial LPS and yeast B-glucans which bind to CR3, (v) for neutrophils, antibody to OX42, an antigen associated with the iC3b complement receptor, or IL8; (vi) for fibroblasts, mannose 6-phosphate/insulin-like growth factor-beta (M6P/IGF-II) receptor and PA2.26, antibody to a cell-surface receptor for active fibroblasts in mice.

9. A method according to Claim 7 or 8 for the treatment of a disease caused, exacerbated, or maintained by secretion from an inflammatory cell, preferably for treatment of a disease selected from allergies (seasonal allergic rhinitis (hay fever), allergic conjunctivitis, vasomotor rhinitis and food allergy), eosinophilia, asthma, rheumatoid arthritis, systemic lupus erythematosus, discoid lupus erythematosus, ulcerative colitis, Crohn's disease, haemorrhoids, pruritus, glomerulonephritis, hepatitis, pancreatitis, gastritis, vasculitis, myocarditis, psoriasis, eczema, chronic radiation-induced fibrosis, lung scarring and other fibrotic disorders.

10. A method according to Claim 3 wherein the third domain targets the agent to an exocrine cell.

11. A method according to Claim 10 wherein the third domain comprises or consists of a ligand selected from pituitary adenyl cyclase activating peptide (PACAP-38) and an antibody to its receptor.

12. A method according to Claim 10 or 11 for the treatment of a disease caused, exacerbated, or maintained by secretion from an exocrine cell, preferably for treatment of acute pancreatitis, or for treatment of mucus hypersecretion from mucus-secreting cells of the alimentary tract, in particular from mucus-secreting cells of the colon.

13. A method according to Claim 3 wherein the third domain targets the agent to immunological cells.

14. A method according to Claim 13 wherein the third domain comprises or consists of a ligand selected from Epstein Barr virus fragment/surface feature and idiotypic antibody (binds to CR2 receptor on B-lymphocytes and lymph node follicular dendritic cells).

15. A method according to Claim 13 or 14 for the treatment of a disease caused, exacerbated, or maintained by secretion from an immunological cell, preferably for treatment of a disease selected from myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus, discoid lupus erythematosus, organ transplant, tissue transplant, fluid transplant, Graves disease, thyrotoxicosis, autoimmune diabetes, haemolytic anaemia, thrombocytopenic purpura, neutropenia, chronic autoimmune hepatitis, autoimmune gastritis, pernicious anaemia, Hashimoto's thyroiditis, Addison's disease, Sjogren's syndrome, primary biliary cirrhosis, polymyositis, scleroderma, systemic sclerosis, pemphigus vulgaris, bullous pemphigoid, myocarditis, rheumatic carditis, glomerulonephritis

(Goodpasture type), uveitis, orchitis, ulcerative colitis, vasculitis, atrophic gastritis, pernicious anaemia, and type 1 diabetes mellitus.

16. A method according to Claim 3 wherein the third domain targets the agent to cells of the cardiovascular system.

17. A method according to Claim 16 wherein the third domain comprises or consists of a ligand selected from ligands for targeting platelets, preferably thrombin or TRAP (thrombin receptor agonist peptide), or antibodies to CD31/PECAM-1, CD24 or CD106/VCAM-1, and ligands for targeting cardiovascular endothelial cells, preferably GP1b surface antigen recognising antibodies.

18. A method according to Claim 16 or 17 for the treatment of a disease caused, exacerbated or maintained by secretion from a cell of the cardiovascular system, preferably for treatment of disease states involving inappropriate platelet activation and/or thrombus formation, or for treatment of hypertension.

19. A method according to Claim 3 wherein the third domain targets the agent to a cell whose secretions can lead to bone disorders.

20. A method according to Claim 19 wherein the third domain comprises or consists of a ligand selected from the group consisting of, ligands for targeting osteoblasts, preferably calcitonin, and ligands for targeting osteoclasts, preferably osteoclast differentiation factor (TRANCE, or RANKL or OPGL) or an antibody to the receptor RANK.

21. A method according to Claim 19 or 20 for the treatment of a disease caused, exacerbated or maintained by secretion from a cell whose secretions can lead to bone disorders, preferably for the treatment of a disease selected from osteopetrosis and osteoporosis.

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22. A method according to any previous Claim, wherein the agent comprises a first domain that cleaves a prot in selected from SNAP-25, synaptobrevin and syntaxin.

23. A method according to Claim 22 wherein the first domain comprises a light chain of a clostridial neurotoxin, or a fragment, variant or derivative thereof which inhibits exocytosis.

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24. A method according to any previous Claim, wherein the second domain comprises a H_N region of a clostridial polypeptide, or a fragment, variant or derivative thereof that translocates the exocytosis inhibiting activity of the first domain into the cell.

25. A method according to any previous Claim for inhibition of constitutive and regulated release from non-neuronal cells.

26. An agent for inhibiting secretion from a non-neuronal cell, comprising at least first, second and third domains, wherein the first domain cleaves one or more proteins essential to exocytosis, the second domain translocates the first domain into the cell and the third domain binds to a non-neuronal cell.

27. An agent according to Claim 26, wherein the third domain is as defined in any of Claims 4, 5, 7, 8, 10, 11, 13, 14, 16, 17, 19, and 20.

28. A pharmaceutical composition comprising an agent according to Claim 26 or 27 in combination with a pharmaceutically acceptable carrier.

29. Use of an agent according to Claim 26 or 27 in treatment of a disease caused, exacerbated or maintained by secretion from a non-neuronal cell.

30. Use of an agent according to Claim 26 or 27 in manufacture of a medicament for treatment of a disease caused, exacerbated or maintained by secretion from a non-neuronal cell.

31. A nucleic acid construct encoding an agent according to Claim 26 or 27, said construct comprising nucleic acid sequences encoding the first, second and third domains.

32. A nucleic acid construct according to Claim 31, operably linked to promoter and terminator sequences, and optionally regulatory sequences, said promoter, terminator and regulatory sequences being functional in a target cell to effect expression of said agent in said target cell.

33. An agent for use in gene therapy, comprising a nucleic acid sequence encoding a first domain which cleaves one or more proteins essential to exocytosis, and a second domain associated with the nucleic acid sequence which, following administration to a patient, translocates the nucleic acid sequence into a non-neuronal target cell and, when in said non-neuronal target cell, expression of the nucleic acid sequence is effected therein.

34. An agent according to Claim 33, wherein the nucleic acid sequence is operably linked to promoter and terminator sequences, and optionally regulatory sequences, said promoter, terminator and regulatory sequences being functional in the non-neuronal target cell to effect expression of said agent in said non-neuronal target cell.

35. An agent according to Claim 32 or 33, wherein the agent further comprises a third domain for targeting the agent to non-neuronal cell.

36. A method of treating by gene therapy a disease caused, exacerbated or maintained by secretion from a non-neuronal cell, said method

comprising administering to a patient an agent according to any of Claims 33-35.

37. Use of a nucleic acid construct according to Claims 31 or 32, or an agent according to any of Claims 33-35, in the manufacture of a medicament for treating by gene therapy a disease caused by, exacerbated, or maintained by secretion from a non-neuronal cell.

38. A method of treating a disease caused, exacerbated or maintained by secretion from a non-neuronal cell, said method comprising administering to a patient a polypeptide that cleaves one or more proteins essential to exocytosis, or a nucleic acid encoding said polypeptide, to a patient.

39. Use of a polypeptide that cleaves one or more proteins essential to exocytosis, or a nucleic acid encoding said polypeptide, in the manufacture of an agent for treating a disease caused by, exacerbated or maintained by secretion from a non-neuronal cell.